In the past decade, genome-wide studies have revealed that the majority of vertebrate genomes are transcribed and generate large numbers of noncoding RNAs.

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Figure 1: The importance of cyrano for proper embryonic development. Embryos injected with anti-sense morpholinos targeting cyrano show curly tails, small heads (top panel) and enlargement of the nasal placode (arrows; bottom panel).

Long intervening noncoding RNAs (lincRNAs)—RNA molecules defined to be longer than 200 nucleotides—are transcribed by RNA polymerase II, capped, spliced and polyadenylated, yet have little or no protein-coding potential and do not overlap with previously characterized classes of noncoding RNAs. Despite their abundance in the genome, the majority of lincRNAs have no known function or mechanisms of action. Recently several of them have been discovered to be misregulated in cancer or even to be involved in regulating genes implicated in cancer.

To understand developmental functions of lincRNAs, we have identified over 550 lincRNAs in zebrafish, an established model for vertebrate development amenable to rapid genetics. We previously demonstrated that two lincRNAs, megamin and cyrano, are required for proper embryonic development, in particular for brain morphogenesis and neurogenesis (Figure 1) (Ulitsky*, Shkumatava* et al., Cell, 2011). Remarkably, the functions of megamin and cyrano are conserved between zebrafish and mammals, despite rapid evolution that has resulted in little sequence conservation. Our goal is to determine the functions of lincRNAs in vertebrate development.
Identification of the conserved developmental functions of lincRNAs

The majority of lincRNAs are expressed in specific regions of the developing nervous system in zebrafish embryos (Figure 2). Thus, we are particularly interested in the roles that lincRNAs play in establishing cellular complexity in the central nervous system (CNS). We are exploring lincRNA functions by manipulating their gene expression and analyzing the phenotypic consequences of lincRNA perturbations in zebrafish embryos. We are focusing on lincRNAs that exhibit sequence conservation to mammals.

Determination of the molecular mechanisms by which lincRNAs carry out their functions

To unravel how lincRNAs regulate embryonic development, we are investigating the molecular and biochemical mechanisms of lincRNA action by determining their interaction partners and downstream targets. We use two complementary systems, zebrafish embryos and mammalian cell culture, to dissect the cellular roles of lincRNAs with important biological functions, such as megamind and cyrano. The powerful combination of zebrafish genetics, molecular and cellular biology, genome-wide approaches and bioinformatics allows us to address whether lincRNAs employ mechanisms of action similar to other noncoding RNAs such as microRNAs.

Investigation of the relationship between lincRNA synteny and function

lincRNAs represent a rapidly evolving group of important developmental regulators: only around 5% of zebrafish lincRNAs have

Figure 2: Tissue-specific expression of lincRNAs by in situ hybridization in zebrafish embryos.
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detectable sequence conservation with mammalian lincRNAs. However, lincRNAs appear more often in conserved genomic positions (synteny) as opposed to protein-coding genes. The enriched appearance of lincRNAs in the syntenic positions indicates that there is an evolutionary pressure to preserve lincRNAs in these positions while the rest of the genome was massively rearranged. Yet the
evolutionary pressures underlying these observations remain unknown.

Hypothesizing that synteny may reflect lincRNA function, we aim to determine why lincRNAs remain in syntenic positions across such disparate species.

Key publications

Year of publication 2019


In-Cell Identification and Measurement of RNA-Protein Interactions
Nature Communications

Year of publication 2018

MicroRNA degradation by a conserved target RNA regulates animal behavior
Nat Struct Mol Biol

Year of publication 2011

Igor Ulitsky, Alena Shkumatava, Calvin H Jan, Hazel Sive, David P Bartel (2011 Jul 28)
Conserved function of lincRNAs in vertebrate embryonic development despite rapid sequence evolution.

Year of publication 2009

Alena Shkumatava, Alexander Stark, Hazel Sive, David P Bartel (2009 Feb 26)
Coherent but overlapping expression of microRNAs and their targets during vertebrate development.
Genes & development : 466-81 : DOI : 10.1101/gad.1745709